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Acute Triethyltin Exposure Effects on the Visual Evoked Potential and Hippocampal Afterdischarge

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16. ABSTRACT

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Acute Triethyltin Exposure: Effects on the Visual Evoked Potential and Hippocampal Afterdischarge[1]

ROBERT S. DYER AND WILLIAM E. HOWELL

Neurotoxicology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

DYER, R. S. AND W. E. HOWELL. *Acute triethyltin exposure: Effects on the visual evoked potential and hippocampal afterdischarge*. NEUROBEHAV. TOXICOL. TERATOL. 4(2) 259–266, 1982.—Acute administration of triethyltin (TET) produces a well-described sequence of pathological events characterized by intramyelinic vacuolation, edema, and histotoxic hypoxia. Recent behavioral studies have attempted to characterize the functional consequences of TET exposures. In this study, the effects of exposure on the visual evoked response (VER) and hippocampal afterdischarge (AD) were determined. Rats were administered either 0, 0.188, 0.375, 0.75, or 1.50 mg/kg TET bromide IP each day for 6 consecutive days. TET increased latencies of P1, N1, P2, N2, and N3 peaks of the VER. The increased latencies are consistent with delayed conduction produced by alterations in the myelin of the optic nerve. TET increased the frequency of spikes within ADs, increased the severity of postictal EEG depressions, and prolonged recovery of excitability following ADs. These effects may be partially explained as reflecting a generalized CNS depression.

Tin Organotin Alkyl tin Triethyltin Neurotoxicity Visual system toxicity
Visual evoked potential Visual evoked response

TRIETHYLTIN (TET) is a neurotoxic substance which produces (1) brain edema [15]; (2) a well described syndrome of myelin splitting [23]; (3) histotoxic hypoxia by uncoupling mitochondrial respiration [1]; and (4) has been an environmental problem [7], accounting for at least one episode of mass poisoning [3].

Several studies have indicated that TET exerts a toxic effect on the visual system [16, 19, 22], and visual disturbances have been reported by individuals exposed to TET (Barnes and Stoner, 1959). Gerren *et al.* [13] noted that mice exposed to high dosages of TET (8 mg/kg) exhibited alterations in the visual evoked response (VER) which were characterized by a gradual lengthening of N1 latencies which reached a maximum 2 hrs following the injection (129% of control) and returned to baseline by 24 hrs. The amplitude of the "earliest response component" was said to be elevated while the "next component" was depressed, but no magnitude, time course, or statistical evaluation of these effects was presented.

The apparent sensitivity of the visual system to TET intoxication and the demonstrated sensitivity of the VER technique for detection of neurotoxicity (e.g., [8]), suggested that a quantitative description of the time course and characteristics of alterations following TET exposure was feasible using the VER technique. The present experiment quantitatively describes the consequences of repeated daily administration of TET upon the VER of adult rats.

In order to provide a more cohesive description of TET's effects upon the functional integrity of the CNS, a system other than the visual system was also investigated. The hippocampal formation was chosen because (1) it is sensitive to disruption by a number of toxicants; and (2) histotoxic hypoxia is one of the consequences of TET exposure [1] and hypoxia produced by acute carbon monoxide exposure produces unique effects upon hippocampal afterdischarges (ADs) [10]. Thus, an additional study was made of the effects of TET upon AD parameters.

METHOD

Forty-seven adult male (60-day old) Long-Evans hooded rats were obtained from Charles River Breeding Co. The animals were individually housed in plastic cages with wood chip bedding in a room with a 12:12 light:dark cycle. Access to food and water was ad lib. The animals were surgically implanted with skull screws overlying the visual cortex (5.5 mm posterior to bregma, 3.0 mm lateral to the midline) and bipolar depth electrodes in the dentate gyrus of the hippocampal formation (2.5 mm posterior to bregma, 2.5 mm lateral to the midline and 3.0 mm below the cortical surface; incisors 5 mm above interaural line) under Chloropent (Fort Dodge Lab., Inc.) anesthesia. Following a week of recovery, the experiment was begun. The animals were divided into 5 groups receiving IP injections of either 0.000 (n=9), 0.188

[1]This paper has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

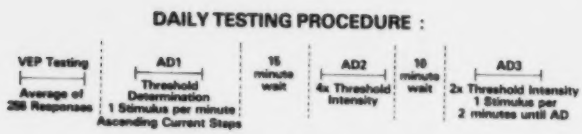

FIG. 1. Daily testing sequence.

(n=9), 0.375 (n=10), 0.75 (n=10), or 1.5 (n=9) mg/kg/day TET bromide in saline. Thus, following the 6 days of dosing, animals had received a total of either 0, 1.125, 2.25, 4.5, or 9 mg/kg TET. The experiment was run in five successive replications with each group represented equally in each replication. The basic paradigm was as follows: On day 1, which was a baseline day, VERs and ADs were determined for all animals. On days 2–7, animals were administered TET (or saline) 2 hours before VER testing. On days 8–10, no injections were given, but VERs and ADs were tested.

Figure 1 illustrates the daily testing sequence. One hour prior to each VER test session, the animals' pupils were dilated with 1% atropine drops. At the time of testing, the animals' head plugs were connected to the recording amplifier (low and high filters set at 0.8 Hz and 1 kHz) by a cable and placed in a small chamber with mirrors on three walls and a Grass strobe lamp on the fourth wall (described more fully in [9]). Thus, although the rat was free to move about the small chamber, it was not possible to escape the light flash. During the test session, four consecutive averaged evoked potentials were obtained. Each average consisted of the response to 64 flashes, presented at 0.5 Hz. The epoch duration was 409.6 msec, and samples were taken every 0.4 msec. Initially, a flash intensity VER property function was planned for each animal each day and thus the four averaged evoked potentials obtained for each animal each day were obtained at four different flash intensities (2, 4, 8, and 16 on the Grass strobe presented in counterbalanced order). However, prior to data analysis, a decision was made that including these intensity settings as variables would increase the number of variables in the study to such a point that it would be difficult to obtain meaningful analyses (5 groups, 5 squads, 10 days, 11 amplitude/latency measurements). Thus, the values obtained from the 4 different intensity settings were averaged together to create 1 value/animal/variable day.

The evoked potential averages were obtained using a Nicolet computer from which X-Y plots were obtained along with digital readouts of peak amplitudes and latencies. Latencies of VER peaks P1, N1, P2, N2, P3, and N3 were obtained. Peak-to-peak amplitudes of P1N1, N1P2, P2N2, N2P3, and P3N3 were also obtained. Figure 2 illustrates the peak designations used here. Immediately following each VER test, the hippocampal AD test was performed.

Hippocampal Afterdischarges

Three ADs were produced in each animal on each test day. The first afterdischarge (AD1) was used to determine the stimulus threshold for AD production. Each animal was stimulated once/min through the bipolar dentate gyrus electrodes with an ascending series of stimulus intensities (20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, and 200 μA) until an AD occurred. Stimulus parameters consisted of a 2 sec train of 50 Hz pulses. Each pulse was a biphasic square wave with 0.2 msec/phase. Fifteen min after the end of AD1, each animal was given a supramaximal stimulus (4 × threshold) to produce AD2. The purpose of AD2 was to ensure that animals had relatively consistent types of ADs, so that their properties could be scored [11]. Ten min after the end of AD2, stimulation was begun to elicit AD3. The purpose of AD3 was to determine the time course of postictal hippocampal hypoexcitability (Swartzwelder *et al.* [21]). Stimuli occurred once every 2 min at twice threshold until AD3 was elicited.

Four types of hippocampal ADs have been described [1]: type 1 consists of an AD followed by a postictal EEG amplitude depression (PID) which is interrupted by a brief rebound AD; type 1a is different from type 1 in that no rebound AD occurs; type 2 consists of an AD followed by no EEG amplitude depression, but with irregular spikes occurring during the postictal period; type 2a differs from type 2 in that no postictal spikes occur.

The following measures were obtained for AD2: pre-AD integrated EEG; AD type; AD duration; number of wet dog shakes (WDS); EEG spike frequency; and PID magnitude. EEG spike frequency was counted in three separate 3-sec blocks: beginning, middle, and end of AD. These 3 blocks were then subtracted from the corresponding values obtained on day 1 to provide a measure of change from pre-TET values. PID magnitude was estimated by connecting the amplified EEG to an integrator. On day 1, the sensitivity of the integrator was adjusted so that during a period of normal EEG (i.e., before stimulation), it reached its maximum and reset about 10 times/min. The number of resets occurring for 5 consecutive min following the AD was then determined. In order to adjust for individual differences in prestimulation EEG resets, resets obtained during each post-AD min were converted to percentages of the prestimulation value occurring on day 1 of the study.

The variable recorded for AD3 was: number of stimuli until AD3 was elicited (a minimum duration of 5 sec was required for a given AD to be counted).

After several days of TET administration, some animals in the 1.5 mg/kg group began to lose weight. To help maintain these animals through the experiment, they were given 5 ml sweetened condensed milk by gavage daily until they showed signs of recovery.

To further reduce the data prior to analysis, three blocks were created by pooling the values obtained on days 2–4, 5–7, and 8–10. The VER data were divided into two sets: latency and amplitude. The latencies and amplitudes were all converted to difference scores from day 1 values. These data sets were subsequently analyzed using MANOVAs. Since two sets of MANOVAs were performed, a Bonferroni correction [7] was applied, such that each MANOVA α was set at 0.025 to keep the overall α at 0.05. Within each data set, MANOVAs were performed on the effects of (1) dosage; (2) day block; (3) squad; and (4) the interaction of dosage × day block. Thus, within each data set, the required level of significance for a given MANOVA was 0.025/4=0.0063. Significant MANOVAs were followed with ANOVAs with α=0.01 (0.05/5) for amplitudes and 0.008 (0.05/6) for latencies. Significant ANOVAs were then followed by Duncan's multiple range test (α=0.05). The overall α for the experiment was therefore 0.05.

The AD data set was treated in a similar manner. A single set of MANOVAs was performed as described above. Since there was no simple dichotomy available to divide the 13 variables obtained from the AD study into 2 smaller groups

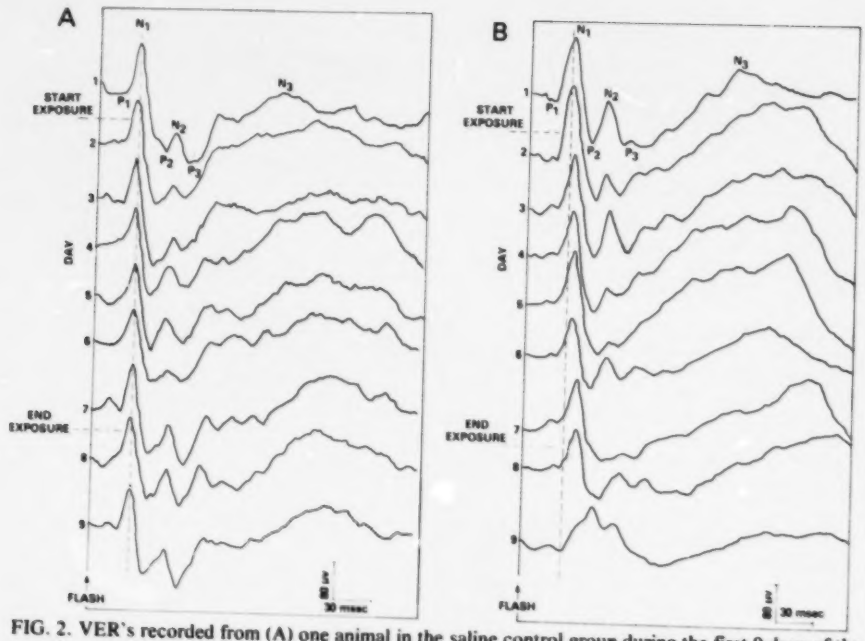

FIG. 2. VER's recorded from (A) one animal in the saline control group during the first 9 days of the experiment; and (B) one animal in the 1.5 mg/TET/kg/day dosage group during the first 9 days of the experiment. Each tracing is a mean of 64 responses to a flash (setting 16 on the Grass strobe unit). Peak designations used in this study are indicated on the day 1 waveform.

of variables for purposes of MANOVA, significant MANOVAs were followed by ANOVAs with α set at 0.0038 (0.5/13). Again, significant ANOVAs were followed by Duncan's multiple range test (α=0.05).

Histology

Following these studies, all animals were perfused with potassium ferrocyanide in Formalin, a 1.0 mA 5 sec pulse was passed through each electrode tip to aid in electrode tip localization, and the electrodes and brains were removed. Cresyl violet-stained sections were used to confirm electrode localization.

RESULTS

The most readily apparent effects of TET were to increase VER latencies and prolong the period of postictal hippocampal hypoexcitability (increase the number of stimuli required to elicit AD3). However, statistical analysis revealed a number of other significant effects, as described below.

Electrode Localization

The electrode placements were generally accurate. Forty-three animals had electrodes clearly located in the hippocampal formation. Of these, 38 were located in the dentate gyrus and 5 were in CA1. One electrode was definitely misplaced (corpus callosum) and in 3 animals the histological preparation did not permit electrode localization. Only the one animal with a clearly misplaced electrode (from the 0.188 mg/kg/day group) was excluded from the AD analysis.

Visual Evoked Response

Alterations in the VER produced by TET are illustrated in Fig. 2, which contains the VER from one rat in the 1.5 mg/kg/day dosage group and one rat in the 0 mg/kg/day dosage group. This figure shows the increased latencies produced by TET. Supporting statistics for the obviously increased latencies may be found in Table 1. Significant dosage × day interactions (Table 1) are accounted for by the gradually increasing latencies produced by TET. Although determining the time course of recovery from TET was not within the design of the study, 4 rats in the 1.5 mg/kg/day dosage group had VERs recorded on days 10, 15, 20, 25, and 150 following the onset of the experiment. Figure 3 illustrates the results for the N1 latency measurement. TET continued to increase N1 latency until day 10. Recovery eventually occurred, but the time course was prolonged. The pattern of changes obtained with the N1 latency was similar to those obtained with other latencies. Figure 4 illustrates the main effect of TET upon latencies of VER peaks P1, N1, P2, N2, and N3. Only the N3 latency was affected at a dosage below 1.5 mg/kg/day. This peak appeared most sensitive to TET, since it was affected at the lowest dosage (0.188 mg/kg/day)

The only VER amplitude which was significantly affected by TET was N2P3. While N2P3 amplitudes decreased slightly in normal animals over days, TET increased N2P3 amplitudes. The increase was only statistically significant at the 0.75 mg/kg/day dosage. Both N1P2 and P2N2 amplitudes increased significantly over days in a manner which was not related to TET exposure.

Hippocampal Afterdischarge

Figure 5 illustrates a typical hippocampal AD. An unexpected consequence of the 3 AD/day procedure was a blurring of the distinctions between AD types. The 15 min separation between AD1 and AD2 was clearly not enough to permit full recovery. Thus, although a 4 × threshold stimulus

TABLE 1

STATISTICAL SUMMARY OF EFFECTS OF TET ON VERs

Source	Latency Analyses							Amplitude Analyses					
	MANOVA F (*df*)	ANOVA F's*						MANOVA F (*df*)	ANOVA F's*				
		P1	N1	P2	N2	P3	N3		P1N1	N1P2	P2N2	N2P3	P3N3
Dosage	9.88 (24,402)†¶	46.8†¶	42.47†¶	9.43†¶	5.37†§	1.38	21.77†¶	2.68 (20,385)†¶	1.73	2.23	0.88	4.35†‡	3.09
Day	3.88 (12,230)†¶	14.13†¶	16.65†¶	3.74	0.07	0.29	2.32	4.08 (10,232)†¶	1.70	5.44†‡	10.78†¶	0.08	0.65
Squad	4.75 (24,402)†¶	5.06†§	2.37	3.73†‡	3.34	3.30	14.71†¶	1.72 (20,385)	—	—	—	—	—
Dosage × Day	2.23 (48,569)†¶	9.45†¶	12.72†¶	5.0†¶	2.59	0.56	4.98†¶	0.60 (40,508)	—	—	—	—	—

*All ANOVA denominator *df* s=120. Numerator *df* s are: dosage (4); day (2); squad (4); and dosage × day (8).
†Considered significant following appropriate Bonferroni correction.
‡$p<0.01$.
§$p<0.001$.
¶$p<0.0001$.

should have invariably produced ADs followed by profound depressions [11], the depressions were often unimpressive. Rebound ADs, which normally occur during the postictal depression following a type 1 AD, were seen in the absence of profound depressions. Due to resulting ambiguity of classification, AD type was not included in the analyses.

Compared to day 1 values, AD thresholds tended to increase. The increase in AD thresholds was significantly less for the 0.188 mg/kg/day group than for any other group, including control. The threshold increase obtained by the 0.750 mg/kg/day group was significantly greater than the control increase. Thus, the effects of TET appear to be biphasic. These results are shown in Fig. 6.

Repeated TET administration appeared to have a biphasic effect upon magnitude of the PID as well; however, this appearance was not supported by the statistical analysis. Figure 7 illustrates the post-AD activity as a percentage of the day 1 pre-AD activity. The low dosage groups (0.188 and 0.375 mg/kg/day TET) appeared to recover more rapidly than the control group, but this apparent facilitation by TET was not statistically significant. Both of the high dosage groups (0.750 and 1.500 mg/kg/day TET) had depressed post-AD activity. The 0.750 mg/kg/day group differed significantly from control only during min 4, but the 1.500 mg/kg/day group differed significantly from control during all 5 min.

Although TET did not significantly alter duration of the AD, it did increase the frequency of spikes which occurred during the AD. Figure 8A shows the effect of TET upon AD spike frequency during the first 3 sec of the AD. The 0.375, 0.750 and 1.500 mg/kg/day groups had significantly elevated spike frequencies.

Analysis of postictal hypoexcitability (number of stimuli to AD3) indicated a biphasic effect of TET. Figure 8B indicates that low dosages decreased while high dosages increased the number of stimuli required to elicit the third AD. The decrease was significant for the 0.375 mg/kg/day group, and the increase was significant for the 1.500 mg/kg/day group. MANOVA and ANOVA summaries are presented in Table 2.

DISCUSSION

Acute exposure to TET significantly altered both the VER and the hippocampal AD.

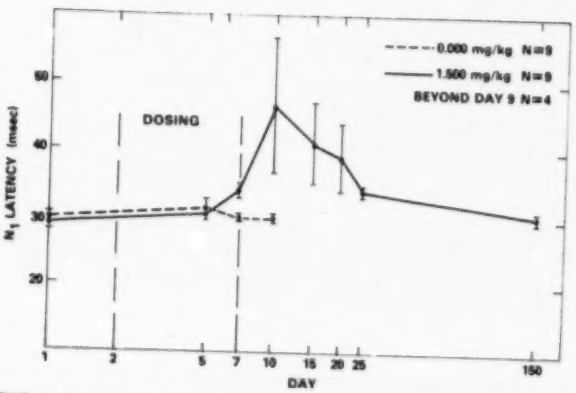

FIG. 3. Time course of changes in N1 latency following administration of 1.5 mg/kg TET daily on days 2–7. N1 latency continued to increase following termination of dosing and did not recover until after day 25.

Visual Evoked Responses

Latencies observed for all VER peaks except P3 gradually increased at the 1.5 mg/kg/day dosage. Increased latencies are consistent with abnormalities in myelin since such abnormalities would be expected to slow conduction velocity. The absence of significant alterations in the amplitudes of the P1N1 and N1P2 components suggests that the population of fibers in the optic nerve has not been reduced. Amplitude of these components has been shown to be closely related to stimulus intensity and, therefore, presumably to number of activated fibers as well [12].

Although TET did alter the latency of early peaks, the late VER component appears to have been the most sensitive detector of toxicity. The N3 latencies were significantly increased over the entire post day 1 test period (i.e., no dosage × day interaction) at the lowest dosage (0.188 mg/kg/day). The influence of TET upon N3 latency was not related to dosage in a linear fashion since the 0.75 mg/kg/day group did not differ significantly from controls, whereas groups receiv-

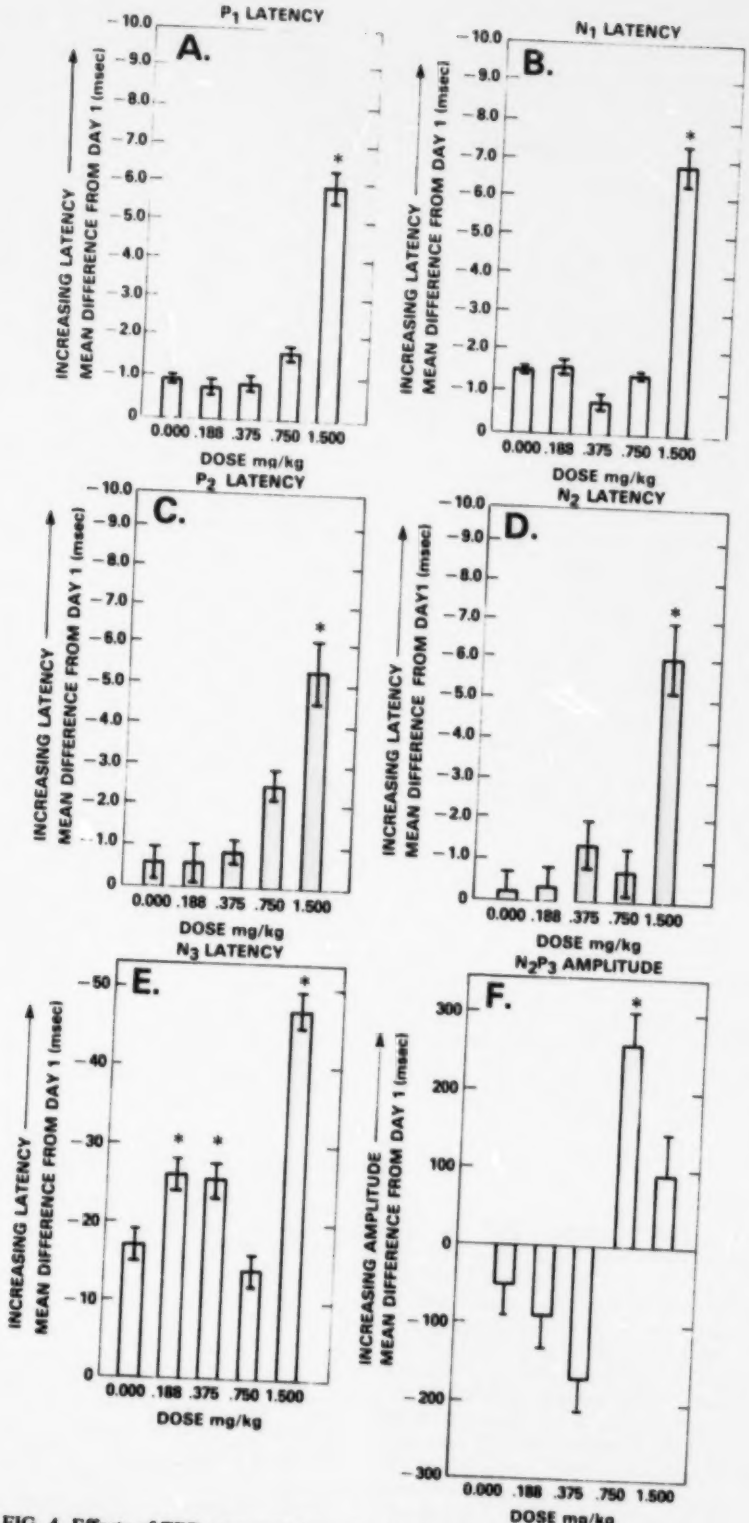

FIG. 4. Effects of TET upon peak latencies of the VER, collapsed across days. TET increased latencies of P1, N1, P2, N2 and N3.

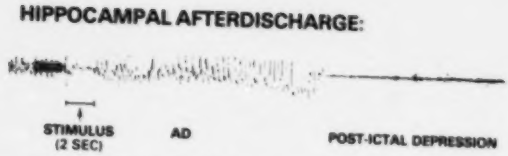

FIG. 5. Typical hippocampal AD.

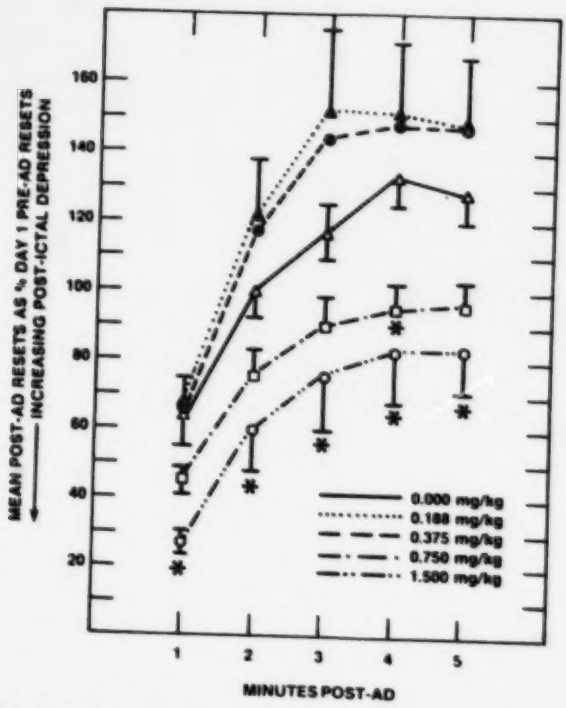

FIG. 7. Effects of TET on postictal (AD2) EEG depression. Magnitude of post-AD depression was calculated using integrated EEG activity. Each time the integrator reached its maximum value and reset, 1 count was recorded. During each post-AD minute, the number of counts/animal was converted to a percentage of the number of counts that animal had during the min prior to AD2 or day 1. In this figure, these percentages are collapsed across days.

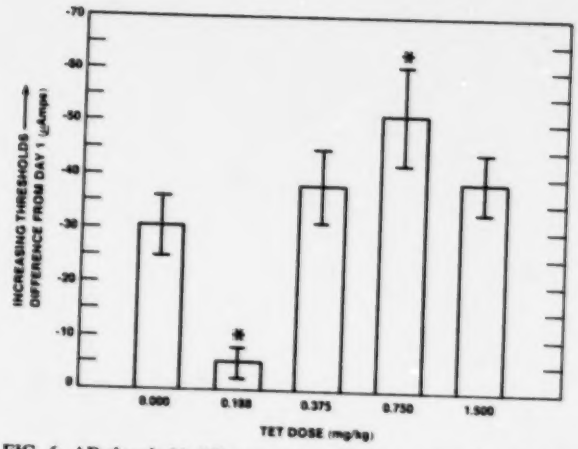

FIG. 6. AD threshold differences from day 1 as a function of TET dose. Thresholds generally increase over days. The increase was significantly smaller than control for the 0.188 mg/kg/day group and larger than control for the 0.750 mg/kg/day group.

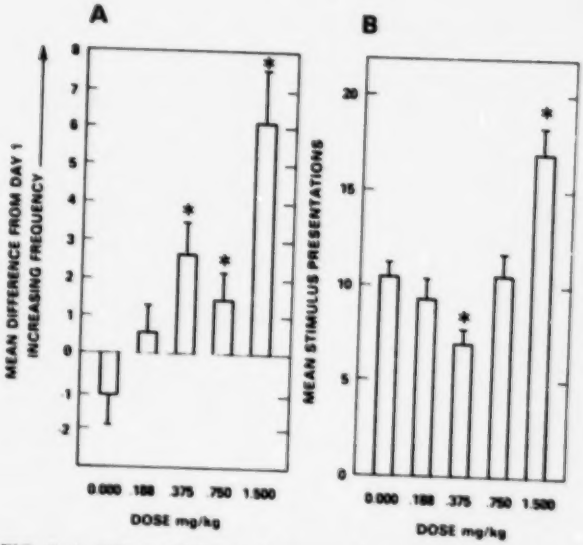

FIG. 8. A. Effects of TET on frequency of spikes occurring during the first 3 sec of the AD. Values plotted are means of the differences obtained between day 1 and all other days. TET significantly increased spike frequency in the 0.375, 0.750 and 1.500 mg/kg/day groups. B. Postictal hypoexcitability, measured as the number of stimulus train presentations required to elicit AD3.

ing both more and less than 0.75 mg/kg/day TET did differ significantly from control. There may be a relationship between the observations that (1) only the N3 latency of the 0.75 mg/kg/day group was not different from control and (2) only the N2P3 amplitude of the 0.75 mg/kg/day group was different from control. The relationships among the different VER components are poorly understood, but it is likely that the morphology of one wave influences the morphology and thereby the latency of the subsequent wave. Thus, the failure of N3 to differ from control at 0.75 mg/kg/day TET may have been secondary to the alterations in N2P3 amplitude at this dosage. The N2P3 amplitude alterations nevertheless remain unexplained. This section of the VER is generally considered to reflect nonspecific thalamic and reticular input [5].

The VER data provide physiological correlates (increased early peak latencies) of TET-induced optic nerve myelinopathy. They also suggest that the optic nerve is not the most sensitive visual system structure, since N3 latency, which presumably reflects cortical activity, was affected at lower dosages than more direct measures of optic nerve function (e.g., P1 and N1 latency).

TABLE 2

STATISTICAL SUMMARY OF EFFECTS OF TET ON ADs

MANOVA

Dose	Day	Day × Dose
F(52,1283)=4.93 $p<0.0001$	F(91,2165)=1.22 $p>0.08$	F(364,4019)=0.81 $p>0.90$

ANOVA (dose effect only; all *df*'s 4,323)

Threshold	F= 5.71* $p<0.0002$	AD Spike Frequency First 3 sec	F=7.43* $p<0.0001$	Integrator Resets Pre AD	F=1.92 $p>0.100$
AD Duration	F= 3.42 $p<0.0093$	Second 3 sec	F=7.69* $p<0.0001$	Post AD min 1	F=7.75* $p<0.0001$
Wet Dog Shakes	F= 2.95 $p<0.02$	Third 3 sec	F=3.60 $p<0.0069$	min 2	F=5.41* $p<0.0003$
Stim to AD3	F=18.41* $p<0.0001$			min 3	F=6.50* $p<0.0001$
				min 4	F=7.26* $p<0.0001$
				min 5	F=7.30* $p<0.0001$

*Significant (Critical Value 0.05/13=.0038).

Finally, these results are not easily understood as consequences of the histotoxic hypoxia which is produced by TET. Previous studies have indicated that an early acute VER response to hypoxia is increased P1N1 amplitude [9], followed at more severe hypoxia by increased N1 and P2 latency and decreased P3N3 amplitude. Since P1N1 amplitudes were not increased, it is unlikely that the present results can be explained in terms of hypoxia.

Hippocampal Afterdischarges

TET appeared to have both excitatory and inhibitory effects upon hippocampal ADs, and the effects of TET upon some hippocampal AD parameters appeared to be biphasic in nature. Thus, low dosages of TET produced less than the normal control increase in AD threshold, decreased the number of stimuli required to elicit a third AD (decreased postictal hypoexcitability), and increased (but not significantly) the rate of recovery from postictal depression. These effects might all be attributed to increased excitability following low levels of TET. Both low (0.375 mg/kg/day) and high (1.5 mg/kg/day) dosages of TET increased spike frequency during the first 3 sec of the AD, a finding which is indicative of increased excitability. On the other hand, exposure to high levels of TET depressed the postictal depression beyond its normal values (0.75 and 1.5 mg/kg/day), increased the number of stimuli required to elicit a third AD (1.5 mg/kg/day), and increased the AD threshold (0.75 mg/kg/day), findings which suggest neuronal depression. Two classical CNS depressants, ethanol and sodium pentobarbital [11,20], increase AD thresholds and decrease AD durations and spike frequency. Only the increased spike frequency at 1.5 mg/kg/day prevents the conclusion that high dosages of TET produce an anesthetic-like neuronal depression. Whatever the mechanisms of TET induced depression in ADs, they are dissimilar to those produced by ethanol and pentobarbital. These results are also dissimilar to those obtained following acute hypoxia produced by carbon monoxide which decreased AD spike frequency [10].

In conclusion, both the VER and hippocampal AD techniques appear sensitive to the acute effects of TET. The VER changes are consistent with myelinopathy and/or CNS depression. Latency of the N3 peak was the most sensitive VER measurement, increasing significantly at a dosage of 0.188 mg/kg TET. TET-induced AD changes are indicative of both excitatory and inhibitory effects. Change in threshold was the most sensitive AD measurement, since it was significantly less than saline control at a dosage of 0.188 mg/kg TET. Some of these effects, especially those on VER latencies, may be explained by the effects of TET on myelin. It does not appear likely that cytotoxic hypoxia produced by uncoupling oxidative phosphorylation can explain the others. It therefore seems likely that TET produces as yet undescribed effects upon the CNS.

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